

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|--|--|--|---|
| <p>(51) International Patent Classification 5 : C08L 67/04, C08G 63/08, 63/64</p> | | <p>A1</p> | <p>(11) International Publication Number: WO 94/11441 (43) International Publication Date: 26 May 1994 (26.05.94)</p> |
| <p>(21) International Application Number: PCT/NL93/00235 (22) International Filing Date: 8 November 1993 (08.11.93)</p> | | <p>(74) Agent: SMULDERS, Th., A., H., J.; Vereenigde Octrooibureaux, Nieuwe Parklaan 97, NL-2587 BN The Hague (NL).</p> | |
| <p>(30) Priority data: 9201949 6 November 1992 (06.11.92) NL</p> | | <p>(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> | |
| <p>(71) Applicant (<i>for all designated States except US</i>): RIJKSUNIVERSITEIT TE GRONINGEN [NL/NL]; Broerstraat 5, NL-9712 CP Groningen (NL).</p> | | <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> | |
| <p>(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>) : GRIJPMAN, Dirk, Wybe [NL/NL]; JOZIASSE, Conrnelis, Aarnoud, Peter [NL/NL]; NIJENHUIS, Atze, Jan [NL/NL]; PENNINGS, Albert, Johannes [NL/NL]; Rijksuniversiteit te Groningen, Broerstraat 5, NL-9712 CP Groningen (NL).</p> | | | |
| <p>(54) Title: RUBBER-MODIFIED POLYLACTIDE AND/OR GLYCOLIDE COMPOSITION</p> | | | |
| <p>(57) Abstract</p> <p>The invention relates to a rubber-modified composition, comprising a matrix and a separate rubber phase, the matrix being based on lactide and/or glycolide (co)polymers, comprising at least 5 wt. % based on the composition of a degradable rubber phase, present as a separate phase, with a glass transition temperature of at most 10 °C, the elongation at break of the composition being at least 120 %. Preferred rubbers are caprolactone or trimethylene carbonate polymers which are blended or block copolymerized with the matrix polymer.</p> | | | |

FOR THE PURPOSES OF INFORMATION ONLY

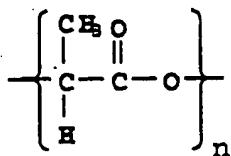
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
|----|--------------------------|----|---|----|--------------------------|
| AT | Austria | GB | United Kingdom | MR | Mauritania |
| AU | Australia | GE | Georgia | MW | Malawi |
| BB | Barbados | GN | Gulnea | NE | Niger |
| BE | Belgium | GR | Greece | NL | Netherlands |
| BF | Burkina Faso | HU | Hungary | NO | Norway |
| BG | Bulgaria | IE | Ireland | NZ | New Zealand |
| BJ | Benin | IT | Italy | PL | Poland |
| BR | Brazil | JP | Japan | PT | Portugal |
| BY | Belarus | KE | Kenya | RO | Romania |
| CA | Canada | KG | Kyrgyzstan | RU | Russian Federation |
| CF | Central African Republic | KP | Democratic People's Republic of Korea. | SD | Sudan |
| CG | Congo | KR | Republic of Korea | SE | Sweden |
| CH | Switzerland | KZ | Kazakhstan | SI | Slovenia |
| CI | Côte d'Ivoire | LI | Liechtenstein | SK | Slovakia |
| CM | Cameroon | LK | Sri Lanka | SN | Senegal |
| CN | China | LU | Luxembourg | TD | Chad |
| CS | Czechoslovakia | LV | Latvia | TG | Togo |
| CZ | Czech Republic | MC | Monaco | TJ | Tajikistan |
| DE | Germany | MD | Republic of Moldova | TT | Trinidad and Tobago |
| DK | Denmark | MG | Madagascar | UA | Ukraine |
| ES | Spain | ML | Mali | US | United States of America |
| FI | Finland | MN | Mongolia | UZ | Uzbekistan |
| FR | France | | | VN | Viet Nam |
| GA | Gabon | | | | |

Title: Rubber-modified polylactide and/or glycolide composition

This invention relates to a rubber-reinforced polylactide and/or polyglycolide composition. Such compositions are known from some recent publications. Polylactide compositions, i.e., synthetic materials based on a matrix of a polylactide,

5



are known for their good degradability in the environment. For this reason, a great deal of research has already been conducted 10 into the preparation and modification of such compositions, for instance for packaging purposes.

In view of the good biocompatibility of a number of lactide polymers, a great deal of research has also been conducted into the applicability of such materials in the biomedical field, 15 such as systems for the controlled delivery of pharmaceuticals or as bioresorbable material.

An extensive overview of the state of the art in the field of polylactide compositions is given in the introduction of WO-A 92/04413, which publication is directed to packages of rapid 20 biodegradation. This publication also mentions the possibility of modifying the lactide compositions with a rubber.

Rubber modification of lactide compositions is also described in WO-A 90/01521 of the same applicant as WO-A 92/04413.

25 In these publications, the starting materials are rubbers based on polyester or copolymers of ethene, propene and various vinyl monomers. Specific mention is made of the use of Hytrel™, a segmented polyester block copolymer of Dupont. The use of such rubbers for the modification of lactide compositions, it is true, leads to an improvement of the impact resistance, but this 30 improvement is not spectacular. From the examples of WO-A 92/04413 it is already evident that with mixtures of different

lactide polymers an improvement of substantially the same magnitude can be achieved. A major disadvantage of the rubber-modified lactide compositions described is that they are hardly biodegradable anymore, if at all, and the biocompatibility 5 leaves to be desired as well. The use of such compositions in the biomedical field and in situations where biodegradability plays an important role is therefore not quite well possible.

The object of the present invention is primarily to provide a polylactide composition which is modified with rubber, which 10 composition possesses clearly improved mechanical properties, such as toughness and elongation at break. A further object of the invention is to provide a polylactide composition which is controllably biodegradable and further possesses good biocompatibility.

15 Accordingly, the present invention relates to a rubber-modified composition, comprising a matrix and a separate rubber phase, the matrix being based on lactide and/or glycolide (co)polymers, comprising at least 5 wt.% based on the composition of a degradable rubber phase, present as a separate 20 phase, with a glass transition temperature of at most 10°C, the elongation at break of the composition being at least 120%.

Surprisingly, it has been found that such compositions exhibit an excellent combination of properties and can also be suitably used as bioresorbable materials. The articles obtained 25 from the compositions according to the invention combine good impact resistance with good biocompatibility, which renders the materials very suitable for use in the manufacture of various sorts of implants.

An essential aspect of the invention is the nature of the 30 rubber which is used for the modification. Most broadly, it has been found a rubber can be used which is degradable. By this is meant that the rubber phase decomposes in the body or in the environment. The decomposition involved here is preferably a decomposition into substantially non-toxic, water-soluble, 35 preferably cell-metabolizable components.

The decomposition can take place under physiological conditions, under the influence of water, bacteria, enzymes and

the like. Such decomposition can also take place in the environment, for instance in the ground. Further, it is advantageous if the rubber itself is also biocompatible.

Another important aspect of the rubber is that it must give to the composition an elongation at break of at least 120%. It has been found that if this requirement is satisfied, the composition possesses the advantageous properties which were mentioned in the foregoing. This requirement is more or less equivalent to the requirement that the rubber have a molecular weight of at least 30 000, more particularly at least 45 000. The upper limit of the elongation at break may be particularly high, it being noted, however, that too high an elongation at break (at 20°C) generally indicates that the composition threatens to lose the lactide properties and starts exhibiting a rubbery behavior.

According to the invention, both mixtures of rubber and matrix polymer and a rubber phase and matrix polymer chemically bound to each other can be used. The chemically bound rubber phase and matrix polymer is preferred. It is noted that when blends are used, to obtain the desired elongation at break, the molecular weight of the rubber must generally be higher than in the case where systems are used in which the rubber phase is chemically bonded to the matrix.

According to the invention, the modification of the lactide matrix with a rubber phase can be carried out in various ways. The rubber can be a homopolymer, a copolymer, or a block copolymer which may or may not be segmented. The monomers from which the rubber phase is made up are chosen from cyclic esters and cyclic carbonates such as ϵ -caprolactone and trimethylene carbonate. Other comonomers can be used as well, one requirement applying to all monomers being that the glass transition temperature must satisfy the requisite value.

When a segmented block copolymer based on hard and rubbery segments is used, it appears that the material possesses two clearly distinguishable glass transition temperatures. Generally, the rubbery blocks will be present as a separate phase, whilst the hard blocks function as a kind of physical

bonding sites for the matrix. In that case, the nature of the hard blocks should satisfy the requirements of the matrix with regard to composition. It is noted that, according to the invention, preferably two, and not more than two, phases are present in the composition. The three-phase systems disclosed in US-A 4,719,246 are not encompassed by the present invention, since the combination of stereocomplexing of the lactide matrix described therein presents problems with regard to the melting temperature. As appears from the examples of the patent application mentioned, the compositions described therein moreover possess a very low elongation at break, which is an indication of the fact that the properties of the material are not particularly good.

According to a preferred embodiment of the invention, as rubber, a block or star copolymer is used. These polymers are preferably chemically bound to the matrix. This can for instance be suitably realized by preparing, in a first step, the rubber phase from cyclic esters and/or carbonates starting from a polyol as initiator. After completion of the rubber polymerization, an OH-functional rubber is obtained, to which rubber the matrix can be fixedly polymerized. Utilizing this method, a chemical bond is obtained between the matrix phase and the rubber phase in a way giving rise to a particular combination of properties. Each molecule then consists of a rubber core with a number of matrix molecules coupled thereto. These molecules could be represented by the formula $(B(A_n))_n$, wherein B represents the rubber part and A the matrix polymer. n designates the functionality of the rubber and has a value of at least 2. The upper limit is not very critical and can be 10 or more.

The rubbers used are preferably homo and copolymers of cyclic esters which are obtained by ring-opening polymerization. Suitable rubbers are based on trimethylene carbonate, ϵ -caprolactone, δ -valerolactone, other cyclic lactones and cyclic carbonates, copolymers thereof and copolymers of such monomers with other suitable monomers, such as D- or L-lactide and glycolide. As initiator for the rubber polymerization,

preferably a polyol with two or more hydroxyl groups, or a polyamine is used. Generally, compounds with active hydrogen atoms are suitable. Suitable polyols include 1,6-hexanediol, glycerol, trimethylolpropane, pentaerythritol, myo-inositol and the like.

Such rubbers are amorphous or have a melting temperature below the body temperature. These rubbers are all incompatible with the polylactide/glycolide matrix, so that phase separation takes place. This is a condition for the realization of an increased impact resistance by rubber modification. The amount of rubber to be used is mainly determined by the desired properties. The lower limit is 5 wt.%, since too little improvement of the properties is obtained at lower contents. The upper limit is not critical and will generally be 75 wt.%, since no additional advantages can be achieved at higher contents. A preferred range for the rubber content is 7.5 to 50 wt.%, since in this range an optimum improvement is achieved while the polylactide properties of the matrix are maintained. The upper limit of the rubber content is preferably 30 wt.%.

The preparation of the rubber should be effected in such a manner that the requirement with respect to the elongation at break of the final composition is satisfied. This requirement means that the rubber should have a comparatively high molecular weight (M_n determined via GPC with polystyrene standard). The preparation of rubbers with a high molecular weight can be effected in the manner known for that purpose, for instance by the use of a catalyst or by choosing the appropriate reaction conditions, such as initiator concentration and reaction time/temperature.

The poly(lactide) matrix to be modified can be a homopolymer of L-lactide, (poly(L-lactide)), or a stereo copolymer of L- and D-lactide, (poly(D,L-lactide)). The L/D ratio determines whether the poly(lactide) is crystalline or amorphous. Copolymers of L/D-lactide with more than 15% D-lactide are amorphous and non-crystallizable. Normally speaking, after compression molding, poly(L-lactide) is semicrystalline but through rapid cooling (quenching) from above

the melting temperature the glass condition can be frozen up, so that the polymer does not crystallize and is amorphous. However, in the course of time or during degradation, possibly this material may still crystallize. Copolymers with less than 15% D-lactide are substantially amorphous after compression molding, but also crystallizable.

For use in biomedical applications, non-crystallizable polymers are preferred, since the crystalline residual products possibly give rise to inflammatory reactions in the body during degradation. The major disadvantage of these amorphous poly(lactides) is the much lower impact resistance compared with the higher crystalline materials. Rubber modification with degradable rubbers is a way of increasing impact resistance. Increasing the toughness and the impact resistance of these poly(lactides) according to the invention can be realized by the synthesis of star-shaped block copolymers of lactide (L- or L/D-lactide) and rubber monomers, as well as by making blends (physical mixtures) of poly(lactide) (L- or L/D-copolymers) and rubber polymers.

The preparation of the lactide and/or glycolide matrix polymers can be effected in known manner, for instance as described in Dutch Patent Application 9000959 or European Patent Application 108,635, the contents of which publications are incorporated herein by reference. In contrast with the disclosure of EP-A 499,204, according to the present invention, no fiber material is used as starting material, but the composition is prepared from monomers by polymerization thereof. It is further noted that the polymerization of the rubber can also be effected in the manner as described in the first-mentioned patent publications. In that case, however, no star polymers but linear polymers are obtained.

The toughness of polymers is an important property, since it represents the amount of energy the material can absorb before break occurs. A measure of the toughness is the area under a force-elongation curve obtained when the tensile strength of a material is measured. In this connection, a high elongation at break is essential to a high toughness. Another

method is to measure the impact resistance of a material, by striking a test rod with a hammer until break occurs. The energy absorbed during the breaking process divided by the original surface area is the impact resistance. Compared with the force-

5 elongation experiment, the speed of an impact test is considerably higher, so that these values rarely correspond.

Impact resistance measurements are performed in accordance with different test standards. Most commonly used is the Izod-notched test (ASTM D-256), whereby the impact resistance is measured on test rods of a depth of 12.7 mm. The unit in which the impact resistance is then expressed is ftlb/inch per inch of notch, or, in SI units, J/m per inch of notch. Because the depth of the rod is constant it can be converted to an energy per unit area J/m².

Measurements on the rubber-modified materials in accordance with this standard enable a comparison with much used commercially available plastics. Our impact resistance

15 measurements were typically carried out in accordance with DIN 53453 (Dynstat unnotched), the advantage of this method being

that only small test pieces are necessary. The impact strength 20 is expressed in J/m². In several cases, measurements were performed in accordance with both standards. The impact strength measured on a notched test piece is always lower than that measured on an unnotched test piece. Our measurements on

crystalline and amorphous compression molded poly(lactide)

25 clearly show the influence of crystallinity on impact resistance. Amorphous poly(lactide), whether quenched poly(L-lactide) or a copolymer of 85/15 20 L/D-Lactide, is significantly less impact resistant than crystalline poly(L-lactide).

30 Both the amorphous non-crystallizable and the crystalline poly(lactides) can be rendered considerably tougher by the rubber modification according to the invention.

ABA block copolymers of 95/5 L/D-lactide with various rubbers possess a much higher impact resistance than the non-35 modified material (20% rubber even gives no break anymore in the Dynstat impact resistance test). The much higher elongations at break (some hundreds of percents) also show that these materials

are particularly tough. A poly(95/5 L/D-lactide) star-block copolymer with a degradable rubber has a particularly high elongation at break and shows no break in the Dynstat impact resistance test. Copolymers of L- and D-lactide can be rendered 5 impact resistant by physically mixing the poly(lactide) with an L-lactide/ ϵ -caprolactone rubber. The impact resistance increases with increasing rubber content and is higher for the copolymers with little or no D-lactide. Amorphous 85/15 L/D lactide 10 copolymers can be rendered impact resistant. Both star-block copolymers and ABA block copolymers and blends with various rubbers or ABA block copolymers yield tough materials which no longer break in the Dynstat impact test at a rubber percentage of approximately 20%. It is remarkable in the comparison of 15 materials modified with equal amounts of the same rubber that the elongation at break of blends is lower than that in block copolymers or star-block copolymers, which points to an important role of the extent of bonding between the rubber part and the lactide matrix. This is the case both for crystalline 95/5 and amorphous 85/15 L/D-lactide modified polymers.

20 The materials according to the invention can be used in all kinds of fields. These uses lie especially in the field where the biological and/or degradation properties are important. Examples of uses include those in the field of packaging materials and in the biomedical field. The materials can be 25 processed into sheets, fibers, articles, hoses, disposables, and the like. The conventional additives can be incorporated in them and processing takes place in the manner known for such polymers.

Possible uses for the materials according to the invention 30 in the biomedical field include their use as drug-release means, nerve conductors, artificial veins, wound covering, artificial skin, sutures, surgical membranes, orthopedic implants and the like.

The invention will now be elucidated in and by a number of 35 examples, without being limited thereto.

EXAMPLES

While employing a number of different starting materials and reaction conditions, a number of rubber-modified synthetic materials were prepared.

Unless otherwise stated, the various materials were polymerized in the following manner.

I. Lactide was polymerized by adding an amount of 10^{-2} mol.% catalyst (Sn-octoate: I^a, tin(II)-bis (2,4-pentanedionato-O-O': I^b) to a melt of the relevant lactide or mixture with lactide at 110°C and polymerizing at this temperature until the polymerization was completed or substantially completed. This method was also followed for the homopolymerization of trimethylene carbonate and ϵ -caprolactone.

II. Block and star-shaped copolymers were obtained by adding a polyol to a melt of a relevant monomer and polymerizing for 12 to 96 hours at 110 to 150°C. Following this polymerization, a melt of the matrix monomers was subsequently added to the rubber formed, where upon polymerization was continued.

The results of the various tests are included in the following Table. In Examples 1-3, a star-rubber based on pentaerithrytol was used, whilst Example 5 is based on an ABA rubber block mixed with the matrix material.

TABLE

| Example | Rubber | Matrix L/D | Preparation | Dynstat kJ/m ² | Izod J/m | σ # | M_n # 10 ⁻³ | Elongation at break % |
|---------|--------------------|---------------|-------------|------------------------------|-------------|------------|-----------------------------|--------------------------|
| 1 | 20% TMC-ε-C1 | 85/15 | II* | (CH ₂ Cl) | g | 25.9 | 73 | 625 |
| 2 | 20% TMC-ε-C1 | 95/5 | II* | (toluene) | g | 34.5 | 73 | 290 |
| 3 | 15% ε-C1/δ-VL | 85/15 | II* | (melt) | g | 22.1 | 120 | 400 |
| 4 | 20% TMC | 85/15 | IIb | (melt) | g | 36.9 | 65.1 | 210 |
| 5** | 21% TMC | 85/15 | II+Ia | (melt) | g | 36.0 | 41.1 | 280 |
| 6 | 20% TMC-ε-C1 | 85/15 | Ia | (blend) | g | 400 | 36.0 | 800 |
| 7 | 34% ε-CL/L-lactide | 100/0 | Ia | | g | 30.8 | 250 | 1500 |
| 8 | 20% TMC-ε-C1 | 85/15 | II | | 44.6 | 41.4 | 46.5 | 120 |
| 9#* | - | 100/0 | Ia | | 10.0 | 83.3 | 72.3 | 7.1 |
| 10#* | - | 85/15 | Ia | | 5.0 | 41.0 | 64.5 | 6.4 |

tensile strength MPA

* Polymerized in the presence of pentaerythritol

** Rubber block copolymer mixed with polylactide matrix

Comparative (M_n matrix > 50,000)

g no break

Rubber block relative to polystyrene standard

CLAIMS

- 1 A rubber-modified composition, comprising a matrix and a separate rubber phase, the matrix being based on lactide and/or glycolide (co)polymers, comprising at least 5 wt.% based on the composition of a degradable rubber phase, present as a separate phase, with a glass transition temperature of at most 10°C, the elongation at break of the composition being at least 120%.
- 5 2. A composition according to claim 1, wherein the rubber is based on trimethylene carbonate.
- 10 3. A composition according to claim 1 or 2, wherein the rubber is based on ε-caprolactone.
- 15 4. A composition according to claims 1-3, wherein the rubber is selected from the group consisting of poly(trimethylene) carbonate, copolymers of L-lactide and ε-caprolactone, glycolide and ε-caprolactone, trimethylene carbonate and ε-caprolactone, δ-valerolactone and ε-caprolactone, as well as rubbers based on a polyol and one or more of the above-mentioned components.
- 20 5. A composition according to claims 1-4, wherein the lacride matrix has been obtained by polymerization in the presence of a star or block rubber.
- 25 6. A composition according to claims 1-4, wherein the polylactide matrix and biodegradable rubber are mixed with each other.
7. A composition according to claims 1-6, wherein the polylactide matrix consists of poly(L-lactide).
8. A composition according to claims 1-6, wherein the polylactide matrix is substantially amorphous and consists of a copolymer of L- and D-lactide with at least 15% D-lactide.
- 30 9. A composition according to claims 1-6, wherein the polylactide matrix is substantially amorphous but crystallizable and is based on a copolymer of D-lactide and L-lactide with less than 15% D-lactide.
10. Use of the composition according to claims 1-9 for medical applications.
- 35 11. Articles manufactured in whole or in part from the composition according to claims 1-9.

12. A method of preparing a composition according to claims 1-
9, comprising polymerizing one or more rubber forming monomers
in the presence of a compound comprising at least one active
hydrogen, so as to form a functional rubber, followed by adding
5 the matrix polymers to the functional rubber and polymerizing
same in the presence of said rubber.

13. A method according to claim 12, wherein a polyol is used as
compound comprising at least one active hydrogen.

INTERNATIONAL SEARCH REPORT

Int. onal Application No.
PCT/03/00235

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C08L67/04 C08G63/08 C08G63/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C08L C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| P, X | <p>MAKROMOLEKULARE CHEMIE, RAPID COMMUNICATIONS, vol.14, no.3, March 1993, BASEL CH pages 155 - 161 D. W. GRIJPMA ET AL. 'STAR-SHAPED POLYLACTIDE-CONTAINING BLOCK COPOLYMERS' see the whole document ---</p> <p>POLYMER BULLETIN, vol.29, no.5, 12 November 1992, HEIDELBERG DE pages 571 - 578 D. W. GRIJPMA ET AL. 'HIGH IMPACT STRENGTH AS-POLYMERIZED PLLA' see page 571 see page 576 ----</p> | 1-5, 7-13 |
| P, X | <p>-----</p> | 1, 3, 4, 7, 10, 11 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 March 1994

Date of mailing of the international search report

25. 03. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Krische, D

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/N/00235

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | MACROMOLECULES, vol.17, no.12, December 1984, EASTON US pages 2764 - 2767 C. X. SONG ET AL. 'SYNTHESIS OF ABA TRIBLOCK COPOLYMERS OF E-CAPROLACTONE AND DL-LACTIDE' see page 2764 see page 2766 - page 2767 --- | 1,3,10, 11 |
| X | DATABASE WPI Week 9231, Derwent Publications Ltd., London, GB; AN 92-255657 & JP,A,4 173 746 (UNITIKA LTD.) 22 June 1992 see abstract | 1,3,6, 10,11 |
| Y | --- | 8,9 |
| Y | WO,A,90 01521 (BATTELLE MEMORIAL INSTITUTE) 22 February 1990 cited in the application see page 45, line 27 - page 46, line 5 see page 76, line 31 - page 77, line 31 see page 82, line 21 - page 83, line 12 --- | 8,9 |
| X | EP,A,0 460 439 (AMERICAN CYANAMID COMPANY) 11 December 1991 see page 2, line 1 - page 3, line 20 see page 9, line 1 - page 10, line 2 see example 5 --- | 1,2,4,7, 10-13 |
| X | EP,A,0 450 777 (DIRECTOR-GENERAL OF THE AGENCY OF INDUSTRIAL SCIENCE AND TECHNOLOGY) 9 October 1991 see claims 1,3 see column 3, line 43 - column 4, line 44 see example 4 --- | 1,3,6, 10,11 |
| A | EP,A,0 427 185 (BOEHRINGER INGELHEIM KG) 15 May 1991 see page 2, line 40 - page 3, line 13 see example 17; table 1 ----- | 1 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Search Application No

PCT/US93/00235

| Parent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|---------|------------------|
| WO-A-9001521 | 22-02-90 | AU-B- | 634723 | 04-03-93 |
| | | EP-A- | 0428620 | 29-05-91 |
| | | JP-T- | 4504731 | 20-08-92 |
| | | US-A- | 5216050 | 01-06-93 |
| | | US-A- | 5180765 | 19-01-93 |
| | | US-A- | 5252642 | 12-10-93 |
| EP-A-0460439 | 11-12-91 | US-A- | 5080665 | 14-01-92 |
| | | CA-A- | 2046192 | 07-01-92 |
| EP-A-0450777 | 09-10-91 | JP-A- | 3290461 | 20-12-91 |
| | | JP-A- | 3290451 | 20-12-91 |
| | | US-A- | 5227415 | 13-07-93 |
| EP-A-0427185 | 15-05-91 | DE-A- | 3937272 | 16-05-91 |
| | | JP-A- | 3177423 | 01-08-91 |